S37-4 Roles of prostanoid receptor signaling in the differentiation and maturation of adipocyte

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Adipogenesis is a crucial aspect in controlling body fat mass. Acquisition of the mature adipocyte phenotype is a highly regulated process in which preadipocytes undergo differentiation, resulting in both an increase in size and number of mature adipocytes in adipose tissue. Prostanoids such as prostaglandin (PG) E_2 and $PGF_{2\alpha}$ have been shown to regulate adipocyte development. PGE_2 exerts its actions through its interaction with four PGE_2 receptor subtypes (EP; EP1, EP2, EP3 and EP4). The diverse actions of PGE_2 can be explained by the existence of these multiple EP subtypes with different signal transduction pathways. Due to the lack of subtype-specific agonists and antagonists, the involvement of each EP subtype in a specific PGE_2 action including suppression of adipocyte differentiation has not been well established until recently. We found that PGE_2-EP4 signaling suppresses 3T3-L1 adipocyte differentiation. Among four EP subtypes, only EP4 receptor is expressed in preadipocytes. PGE_2, an EP4 agonist and dibutylyl cAMP significantly decreased the triglyceride content of cells after differentiation treatment. An EP4-antagonist as well as indomethacin promoted differentiation. These results suggest that the endogenously synthesized PGE_2 via EP4 receptor/cAMP pathway participates in the negative regulation of adipocyte differentiation (Tsuboi *et al.* 2004). Microarray analysis revealed that PGE_2 inhibits a crucial step of the adipocyte differentiation process, including the expression of peroxisome proliferator activated receptor-γ (*Pparg*) and CCAAT/enhancer binding protein-α (*Cebpa*), by acting on the EP4 receptor (Sugimoto *et al.* 2004). We are now examining adipose tissues of EP4-deficient mice under physiological and some pathological settings.